

## Responsiveness of Atrial Natriuretic Factor to Reduction in Right Atrial Pressure in Patients With Chronic Congestive Heart Failure

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In patients with congestive heart failure, atrial natriuretic factor may serve as a counter-regulatory hormone, offsetting the vasoconstrictive and volume-retentive effects of the sympathetic nervous system, the renin-angiotensin-aldosterone system and vasopressin. Indeed, the plasma levels of atrial natriuretic factor and the vasoconstrictor hormones are often simultaneously elevated in these patients. It is not known, however, whether atrial natriuretic factor remains responsive to sudden reductions in atrial pressure in patients with chronic heart failure, or is unresponsive like the vasoconstrictor systems. To examine this issue, the plasma concentrations of atrial natriuretic factor and the vasoconstrictor hormones were measured in 20 normal subjects and 12 patients with chronic congestive heart failure during incremental lower body negative pressure, an intervention that lowers atrial pressure.

In the normal subjects, incremental lower body negative pressure at -10, -20 and -40 mm Hg decreased central venous pressure and pulse pressure. At maximal lower body negative pressure, plasma atrial natriuretic factor levels decreased from  $51 \pm 5$  to  $27 \pm 3$  pg/ml ( $p < 0.01$ ),

whereas increases occurred in plasma levels of norepinephrine ( $194 \pm 11$  to  $385 \pm 70$  pg/ml,  $p < 0.01$ ), renin activity ( $1.4 \pm 0.2$  to  $3.9 \pm 0.1$  ng/ml per h,  $p < 0.01$ ) and vasopressin ( $1.3 \pm 0.1$  to  $6.4 \pm 2.4$  pg/ml,  $p < 0.05$ ). In the patients with congestive heart failure, lower body negative pressure also reduced central venous pressure. Baseline plasma atrial natriuretic factor levels were markedly elevated, averaging  $438 \pm 138$  pg/ml, and decreased to  $317 \pm 87$  pg/ml at maximal lower body negative pressure ( $p < 0.05$ ). In these patients, lower body negative pressure did not change plasma norepinephrine ( $614 \pm 113$  to  $764 \pm 128$  pg/ml), renin activity ( $5.6 \pm 1.1$  to  $5.8 \pm 0.9$  ng/ml per h) or vasopressin ( $4.2 \pm 1.0$  to  $7.2 \pm 1.9$  pg/ml) (all  $p = NS$ ).

Unlike vasoconstrictor hormone secretion, atrial natriuretic factor secretion remains responsive to reductions in atrial pressure. A dynamic role for atrial natriuretic factor would underscore its potential to regulate vascular resistance and sodium excretion during changes in posture or volume status in patients with congestive heart failure.

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Mammalian atria synthesize and secrete a peptide, atrial natriuretic factor, with natriuretic and vasorelaxant properties (1,2). It is well established that sudden changes in atrial pressure can affect atrial natriuretic factor release in normal atria (3-6). In normal humans, sodium loading and passive

leg raising increase, and upright tilt decreases, plasma atrial natriuretic factor levels (7-9). Plasma atrial natriuretic factor concentrations are often elevated in patients with heart failure (10-14). The effect of chronic atrial hypertension, however, on atrial natriuretic factor regulation is not known. This issue is particularly important in patients with congestive heart failure, because atrial natriuretic factor may serve as a counter-regulatory hormone, opposing the vasoconstrictive and volume-retentive effects of the sympathetic nervous system, the renin-angiotensin-aldosterone system and vasopressin.

Normally, the plasma levels of the vasoconstrictor hormones, norepinephrine, angiotensin II and vasopressin, increase during maneuvers that decrease cardiac filling pressures or blood pressure, such as upright posture or volume depletion (15-17). In patients with heart failure, although plasma vasoconstrictor hormone concentrations are often

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elevated, they are not affected by sudden changes in cardiac filling pressures (18,19). Dysfunction of cardiopulmonary and arterial baroreceptors has been reported in both experimental (20-22) and human (23) heart failure and may explain the blunted responsiveness of these hormones to sudden changes in cardiac loading conditions.

The purpose of this study was to determine whether plasma atrial natriuretic factor concentration remains responsive to sudden reductions in atrial pressure or is unresponsive like the vasoconstrictor systems. A dynamic role for atrial natriuretic factor would underscore its potential in regulating vascular resistance and sodium excretion during sudden changes in posture or volume status in patients with congestive heart failure. To examine this issue, the plasma concentrations of atrial natriuretic factor, norepinephrine, vasopressin and renin activity were measured in patients with chronic congestive heart failure during incremental lower body negative pressure, a maneuver designed to suddenly reduce cardiac filling pressures. The results in these patients were compared with those obtained in normal volunteers who were subjected to the same intervention.

## Methods

**Study subjects and patients.** Twenty normal subjects and 12 patients with congestive heart failure participated in this study. The protocol was approved by the Committee for the Protection of Human Subjects from Research Risks at Brigham and Women's Hospital and each subject gave written, informed consent. The normal group comprised 11 men and 9 women, aged 19 to 34 years (mean  $\pm$  SD,  $26 \pm 5$ ). Normalcy was established by history, physical examination and laboratory analysis, which included a blood count, serum glucose concentration and indexes of renal and hepatic function.

**The patients with chronic congestive heart failure** included 10 men and 2 women. Their ages ranged from 46 to 81 years (mean  $63 \pm 9$ ). The cause of heart failure was coronary artery disease in eight patients and primary cardiomyopathy in four. Seven of the patients were in New York Heart Association functional class III and five were in class IV. Left ventricular ejection fraction assessed by radionuclide ventriculography ranged from 7 to 34% (mean  $16 \pm 8$ %). Right heart catheterization was performed in eight of the patients with heart failure within 2 days of this study. In these patients, cardiac index averaged  $2.2 \pm 1.1$  liters/min per  $m^2$  and pulmonary capillary wedge pressure averaged  $33 \pm 8$  mm Hg.

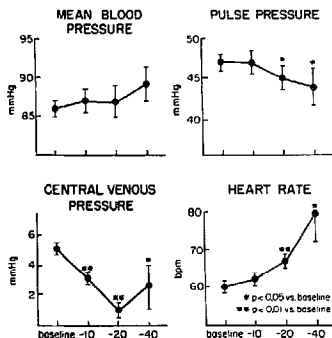
**Experimental protocol.** All studies were conducted in the morning with the patient in the postabsorptive state without premedication. Water was permitted, however, alcohol, caffeine and cigarettes were all prohibited within 12 h of study. Vasodilator and diuretic medications were withheld at

least 24 h before the study. Each study was conducted in a 22°C temperature-controlled laboratory.

On arrival in the laboratory, a polyethylene catheter was inserted percutaneously into an antecubital vein and advanced to the superior vena cava. The catheter was attached to a Gould P-23 pressure transducer and the central venous pressure measurement was displayed on a Gould physiologic recorder. Zero reference was chosen to be at the right atrium, estimated to be 5 cm vertically beneath the sternal angle of Louis. Systolic and diastolic blood pressures were determined by sphygmomanometry with an automated oscillometric technique (Dinamap, model 845XT, Critikon Corp.). Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Mean blood pressure was calculated as the sum of the diastolic blood pressure and one third of the pulse pressure. Heart rate was determined by a simultaneously obtained electrocardiographic signal and calculated from the RR interval. To reduce cardiac filling pressures, each subject was placed in a lower body negative pressure chamber (University of Iowa, Medical Instruments Department). This chamber was sealed at the level of the iliac crest. A commercial vacuum cleaner was used to provide a continuous vacuum source whose intensity was regulated by a rheostat.

After a 30 min stabilization period, baseline hemodynamic data were collected every 15 min for 1 h. At the end of 1 h, blood was collected from the central venous catheter for determination of plasma levels of atrial natriuretic factor, norepinephrine, renin activity and arginine vasopressin. Thereafter, normal subjects underwent 1 h periods of incremental lower body negative pressure at -10, -20 and -40 mm Hg. Patients with congestive heart failure underwent a similar protocol using negative pressure periods of -10 and -40 mm Hg. To maintain patient comfort and cooperation, the protocol was shortened by deleting the -20 mm Hg period. Blood pressure, central venous pressure and heart rate were determined every 15 min during each experimental period. Blood was collected for hormonal assays at the completion of each period. The experiment was terminated prematurely if symptomatic hypotension occurred.

**Hormonal assays.** Blood samples for hormonal assays were placed immediately on ice when collected and were centrifuged at 2°C. Plasma samples were stored at -70°C before assay. Blood samples for atrial natriuretic factor were drawn into chilled vacutainer tubes containing 1.5 mg/ml of ethylenediaminetetraacetic acid (EDTA). Plasma atrial natriuretic factor concentration was measured by radioimmunoassay using a rabbit antibody prepared against synthetic human atrial natriuretic factor. The assay was performed according to the procedure described by Peninsula Laboratories. Synthetic atrial natriuretic factor standards, atrial natriuretic factor [99-126] and  $^{125}$ I-atrial natriuretic factor [99-126] were obtained from Peninsula Laboratories. Assays were performed on Sep-Pak extracted plasma. The intra-assay



**Figure 1.** Hemodynamic responses to lower body negative pressure in 20 normal subjects. All 20 subjects completed the baseline, -10 and -20 mm Hg periods, and 8 completed the -40 mm Hg periods. Values are expressed as mean values  $\pm$  SEM.

say variability in our laboratory is 7.3%. Plasma norepinephrine concentration was quantified by a modified radioenzymatic assay (24). Plasma renin activity and plasma arginine vasopressin concentration were determined by radioimmunoassay (25,26).

**Statistical analysis.** The experimental results are presented as mean values  $\pm$  SEM. For each participant, data from an experimental period were included only if the subject remained in stable condition and completed the 60 min intervention. Thus, all data reported were collected under steady state conditions. The data before and during lower body negative pressure for each group were compared by analysis of variance for repeated measures with trend analysis (27). When the analysis of variance indicated a statistically significant difference, Dunnett's test (28) was used to analyze the difference between two means. Statistical significance was accepted at the 95% confidence level ( $p < 0.05$ ).

## Results

**Hemodynamic response to incremental lower body negative pressure in normal subjects (Fig. 1).** Eight of the 20 normal subjects were able to complete the entire protocol and 12 subjects terminated the protocol after completing the 1 h period of lower body negative pressure at -20 mm Hg. In these latter subjects, increasing lower body negative pressure to -40 mm Hg resulted in symptomatic hypotension.

The baseline systolic blood pressure was  $118 \pm 1$  mm Hg,

diastolic blood pressure was  $71 \pm 1$  mm Hg, mean blood pressure was  $86 \pm 1$  mm Hg and pulse pressure was  $47 \pm 1$  mm Hg. No significant change occurred in systolic, diastolic or mean blood pressure during incremental lower body negative pressure in the subjects who met the criteria for data inclusion. Pulse pressure decreased significantly during the -20 and -40 mm Hg periods to  $45 \pm 2$  and  $44 \pm 2$  mm Hg, respectively (each  $p < 0.05$ ). Baseline central venous pressure was  $5.2 \pm 0.6$  mm Hg. Incremental lower body negative pressure decreased central venous pressure to  $3.5 \pm 0.6$  ( $p < 0.01$ ),  $1.4 \pm 0.7$  ( $p < 0.01$ ) and  $2.5 \pm 1.4$  mm Hg ( $p < 0.05$ ) during the -10, -20 and -40 mm Hg periods, respectively. The mean central venous pressure data during the -40 mm Hg period comprised only the measurements in the eight remaining subjects. Baseline heart rate was  $60 \pm 2$  beats/min. Heart rate accelerated at -20 and -40 mm Hg to  $67 \pm 2$  ( $p < 0.01$ ) and  $79 \pm 7$  beats/min ( $p < 0.05$ ), respectively.

**Hemodynamic response to incremental lower body negative pressure in patients with chronic heart failure (Fig. 2).** Nine of the 12 patients with chronic heart failure completed the entire protocol. In three patients, the protocol was terminated after the patients completed lower body negative pressure at -10 mm Hg because symptomatic hypotension occurred during the -40 mm Hg period. Baseline central venous pressure in these three individuals was 1, 3 and 4 mm Hg, respectively. Baseline systolic blood pressure was  $113 \pm 3$  mm Hg, diastolic blood pressure was  $76 \pm 2$  mm Hg, mean blood pressure was  $89 \pm 2$  mm Hg and pulse pressure was  $37 \pm 3$  mm Hg. Compared with normal subjects, the patients with chronic heart failure had a lower baseline pulse pres-

**Figure 2.** Hemodynamic responses to lower body negative pressure in 12 patients with congestive heart failure. All 12 patients completed the baseline and -10 mm Hg periods, and 9 patients completed the -40 mm Hg period. Values are expressed as mean  $\pm$  SEM.

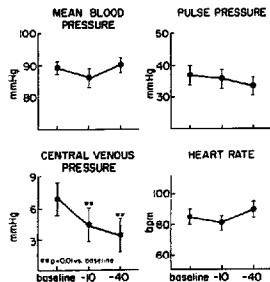
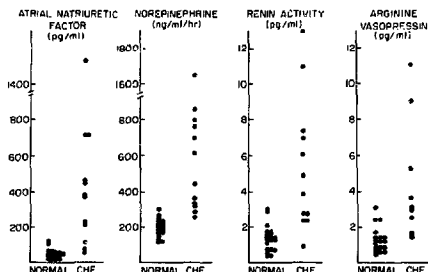


Figure 3. Individual baseline hormonal concentrations in 20 normal subjects and 12 patients with congestive heart failure (CHF).



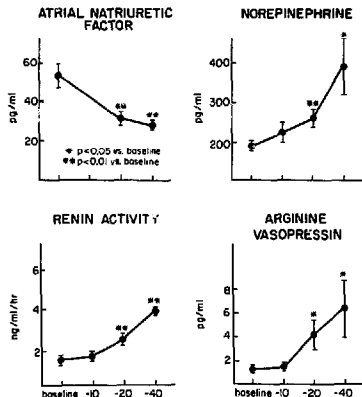
sure ( $p < 0.01$ ). Incremental lower body negative pressure did not alter any of these blood pressure variables. In contrast to the findings in normal subjects, lower body negative pressure did not decrease the pulse pressure in the heart failure group. The baseline central venous pressure was  $6.9 \pm 1.6$  mm Hg. According to the experimental design, incremental lower body negative pressure caused a decrease in central venous pressure at both the  $-10$  and  $-40$  mm Hg stages to  $4.4 \pm 1.6$  ( $p < 0.01$ ) and  $3.4 \pm 1.7$  mm Hg ( $p < 0.01$ ), respectively. Baseline heart rate in these patients was  $84 \pm 5$  beats/min, a value significantly greater than that observed in the normal group ( $p < 0.01$ ). In contrast to the normal subjects, however, no further increase in heart rate occurred in the patients with heart failure during lower body negative pressure.

**Hormonal response to lower body negative pressure in normal subjects (Fig. 3 and 4).** The individual basal values for plasma concentrations of atrial natriuretic factor, norepinephrine, vasopressin and plasma renin activity are illustrated in Figure 3. The hormonal response to incremental lower body negative pressure in the normal group is illustrated in Figure 4. The plasma atrial natriuretic factor in the normal volunteers before intervention averaged  $51 \pm 5$  pg/ml; the level decreased to  $32 \pm 3$  pg/ml during the  $-20$  mm Hg period ( $p < 0.01$ ) and to  $27 \pm 3$  pg/ml during the  $-40$  mm Hg period ( $p < 0.01$ ). Baseline plasma norepinephrine concentration was  $194 \pm 11$  pg/ml. Although no significant change in plasma norepinephrine level occurred during the  $-10$  mm Hg period, the level increased to  $262 \pm 21$  ( $p < 0.01$ ) and  $385 \pm 76$  pg/ml during the periods of  $-20$  and  $-40$  mm Hg, respectively. The initial plasma renin activity at rest in these normally hydrated subjects was  $1.4 \pm 0.2$  ng/ml per h. No change in plasma renin activity occurred during the  $-10$  mm Hg period. However, incremental lower body negative pressure to  $-20$  and  $-40$  mm Hg increased plasma renin activity to  $2.4 \pm 0.3$  ( $p < 0.01$ ) and  $3.9 \pm 0.7$  ng/ml per h ( $p < 0.01$ ), respectively. The baseline plasma

vasopressin concentration was  $1.3 \pm 0.2$  pg/ml. No change in plasma vasopressin concentration was observed during the  $-10$  mm Hg period but the level increased during the  $-20$  and  $-40$  mm Hg periods to  $4.2 \pm 1.2$  and  $6.4 \pm 2.4$  pg/ml, respectively (each  $p < 0.05$ ).

**Hormonal response to lower body negative pressure in heart failure (Fig. 3 and 5).** The individual values for plasma atrial natriuretic factor, norepinephrine, vasopressin and plasma renin activity, and the group hormonal response to

Figure 4. Hormonal responses to lower body negative pressure in 20 normal subjects. Baseline  $-10$  and  $-20$  mm Hg periods include all 20 subjects and the  $-40$  mm Hg period includes 8 subjects. Values expressed as mean  $\pm$  SEM.



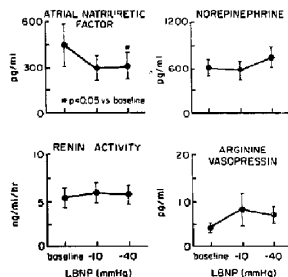


Figure 5. Hormonal responses to lower body negative pressure (LBNP) in 12 patients with congestive heart failure. Baseline and -10 mm Hg periods include all 12 patients and the -40 mm Hg period includes 9 patients. Values are expressed as mean  $\pm$  SEM.

incremental lower body negative pressure in patients with congestive heart failure are displayed in Figures 3 and 5, respectively. Compared with the hormonal values in normal subjects, values in patients with chronic heart failure ranged widely and were frequently elevated. The baseline plasma concentration of atrial natriuretic factor averaged  $438 \pm 138$  pg/ml for the heart failure group, a value significantly higher than that observed in the normal volunteers ( $p < 0.01$ ). As central venous pressure decreased with the application of lower body negative pressure, the plasma atrial natriuretic factor concentration tended to decrease at -10 mm Hg ( $297 \pm 89$  pg/ml,  $p = NS$ ) and then decreased significantly at -40 mm Hg to  $317 \pm 87$  pg/ml ( $p < 0.05$ ).

Baseline plasma norepinephrine concentration was  $614 \pm 113$  pg/ml; baseline plasma renin activity was  $5.4 \pm 1.1$  ng/ml per h and baseline plasma concentration of vasopressin was  $4.2 \pm 1.0$  pg/ml. Each of these values was significantly higher ( $p < 0.01$ ) than the values obtained in the normal subjects. In contrast to findings in the normal subjects, however, incremental lower body negative pressure in patients with heart failure caused no further increase in the plasma levels of norepinephrine, vasopressin and plasma renin activity.

## Discussion

The control of atrial natriuretic factor release in pathophysiologic states is incompletely understood. Although it is clear that sudden changes in atrial pressure in the normal atrium can affect atrial natriuretic factor release, the effect of chronic atrial hypertension on atrial natriuretic factor regulation has not been characterized. This issue is particularly relevant in edema states associated with chronic atrial hy-

pertension, such as chronic congestive heart failure. When administered in pharmacologic doses, atrial natriuretic factor has natriuretic, diuretic and vasorelaxant properties (1,2,29-33). It has been postulated that this peptide may play a counter-regulatory role opposing the vasoconstrictive and sodium- and water-retentive forces, that is, plasma catecholamines, angiotensin II and vasopressin. There have been many questions raised regarding the physiology of atrial natriuretic factor in patients with heart failure. One of these is whether atrial natriuretic factor secretion can be regulated by decreasing atrial pressures or remains static like the vasoconstrictor systems.

**Hormonal response to lower body negative pressure in normal subjects.** Plasma atrial natriuretic factor levels normally increase in response to increases in atrial volume and pressures. Perfusates collected from isolated rat hearts subjected to high central venous pressure have high atrial natriuretic factor levels and demonstrate natriuretic activity (3,4). Plasma atrial natriuretic factor concentration increases in the anesthetized rat and the conscious dog during volume expansion and sodium loading (5,6,34). In normal humans, salt loading and passive leg raising each increase plasma atrial natriuretic factor concentration (7-9). When normal subjects are tilted, particularly after sodium loading, atrial natriuretic factor levels decrease (7-8). Our study is one of the first to demonstrate in humans that reduction in central venous pressure by incremental lower body negative pressure decreases plasma atrial natriuretic factor concentration. Thus, atrial distension stimulates secretion of atrial natriuretic factor whereas reduction in atrial pressure decreases it.

In normal humans, baroreceptors located in the heart, lungs and great vessels respond to sudden changes in posture and volume status by altering the activity of the sympathetic nervous system, the renin-angiotensin-aldosterone system and the hypophyseal secretion of vasopressin. Orthostasis and volume depletion are accompanied by increases in plasma catecholamines, renin activity and vasopressin (15-17), as demonstrated in this study. An increase in these vasoconstrictive and volume-retentive hormones occurred only during the higher levels of lower body negative pressure, when both central venous pressure and pulse pressure were decreased, suggesting that both cardiopulmonary and arterial baroreceptors were unloaded. The simultaneous increases in the vasoconstrictor hormone levels and the decrease in plasma atrial natriuretic factor level act in concert to maintain blood pressure and conserve sodium.

It has been reported (35,36) that phenylephrine, epinephrine, angiotensin II and vasopressin may increase plasma atrial natriuretic factor levels. The increased secretion of atrial natriuretic factor is thought to be a consequence of increased atrial pressure induced by these vasoconstrictors rather than a direct effect of these hormones. In fact, administration of the nonpressor analog of vasopressin does

not increase atrial natriuretic factor levels, and abolishing the pressor response of vasopressin prevents an increase in atrial natriuretic factor concentration (35). Furthermore, neither adrenergic nor muscarinic blockade inhibits the atrial natriuretic factor response to tachycardia or atrial distension (37,38). In the normal volunteers in this study, the changes in atrial natriuretic factor levels during lower body negative pressure were directionally opposite to the baroreceptor-mediated changes in catecholamines, renin and vasopressin. Thus, the decrease in the atrial natriuretic factor during lower body negative pressure cannot be attributed to these neurohumoral mechanisms.

**Atrial natriuretic factor responsiveness in heart failure.** The plasma concentration of atrial natriuretic factor is frequently increased in patients with congestive heart failure (10-14) and appears to correlate with both right and left atrial pressure in these patients (12-14). Whether sudden changes in atrial pressure alter the secretion of atrial natriuretic factor in patients with chronic atrial hypertension has not been previously examined in a systematic manner. Several studies conducted in animals (39) and humans (13,14) suggest that release of atrial natriuretic factor is still responsive to changes in atrial pressure in heart failure. In conscious dogs subjected to thoracic inferior vena cava constriction, which is a model of low output heart failure, decreases in right and left atrial pressure are accompanied by a decrease in plasma atrial natriuretic factor concentration (39). In humans with chronic heart failure subjected to leg raising or exercise, which are maneuvers associated with increased atrial pressure, atrial natriuretic factor concentration increases (13,14).

*In this study, plasma levels of atrial natriuretic factor were substantially higher in the patients with congestive heart failure than in the normal volunteers. Individual values varied widely, and in several patients with heart failure exceeded normal values by 10-fold. Plasma atrial natriuretic factor levels fell when central venous pressure decreased, indicating that chronically stretched atria can still respond to decreases in atrial pressure by reducing atrial natriuretic factor secretion. However, it would be premature to state that the responsiveness of atrial natriuretic factor to reduction in atrial pressure was completely preserved in patients with chronic congestive heart failure until the stimulus-response relations between atrial natriuretic factor and atrial pressures are carefully compared in normal subjects and patients with chronic heart failure. Adaptation of cellular mechanisms of atrial natriuretic factor release and depletion of its stores, altered atrial compliance or efferent neural impulses may blunt the ability of the atria to respond to changes in atrial pressure. In experimental heart failure, the myocardium can express the gene for atrial natriuretic factor (40). Thus, release of atrial natriuretic factor from the failing ventricle may also be pertinent to the observations in this study.*

**Baroreceptor function in congestive heart failure.** In contrast to the decrease in atrial natriuretic factor concentration, plasma levels of norepinephrine, vasopressin and renin activity did not change with lower body negative pressure. Previous studies (18,19,41) in patients with chronic heart failure demonstrated an absent or significantly blunted response of these hormones to maneuvers that reduce cardiac filling pressures, such as lower body negative pressure, orthostasis and nitroprusside infusion. Evaluation of cardiopulmonary and arterial baroreceptors during volume loading, carotid artery occlusion or phenylephrine infusion have shown that the sensitivity of these receptors is blunted in animal models of heart failure (20-22). Baroreceptor dysfunction may, therefore, explain the lack of change in these vasoconstrictor and sodium-retentive hormones in patients with chronic heart failure despite the reduction in central venous pressure caused by lower body negative pressure.

**Physiologic implications.** In normal humans, upright posture and volume depletion cause prompt increases in sympathetic nervous system activity and in secretion of renin and vasopressin, effects that preserve cardiovascular homeostasis and promote restoration of normal volume status. In patients with chronic congestive heart failure, these vasoconstrictor systems are often tonically activated, resulting in excessive vascular resistance and sodium retention. It is postulated that baroreceptor dysfunction contributes to unrestrained vasoconstrictor activity and inability of these systems to modulate changes in blood pressure or body water balance. In contrast, atrial natriuretic factor secretion is not mediated by baroreflex mechanisms. As such, it may function as an ideal counter-regulatory hormone opposing the vasopressor and volume-retentive effects of the vasoconstrictor systems. By remaining responsive to changes in cardiac filling pressure, atrial natriuretic factor may modulate vascular resistance and fluid balance in patients with heart failure.

**Limitations of this study.** Several factors should be considered that may affect interpretation of the data. First, only right atrial pressure, and not left atrial pressure, was used to assess the responsiveness of atrial natriuretic factor during lower body negative pressure. The average right atrial pressure in the patients with heart failure did not seem substantially higher than that in the normal individuals. There was, however, considerable variation in the baseline right atrial pressure among the patients with heart failure. Furthermore, right heart catheterization performed in the majority of the patients with heart failure within 2 days of this study confirmed that the pulmonary capillary wedge pressure was considerably elevated ( $33 \pm 8$  mm Hg; see Methods). Therefore, it is likely that an elevated left atrial pressure contributed to the increased levels of atrial natriuretic factor in the patients with heart failure, and that left atrial pressure decreased during lower body negative pres-

sure, thereby contributing to the decrease in atrial natriuretic factor concentration.

Second, plasma atrial natriuretic factor concentration rather than atrial natriuretic factor secretion rates was measured. Therefore, the changes in plasma atrial natriuretic factor levels may be the result of alterations in secretion or clearance, or both. Furthermore, the measurement of immunoreactive atrial natriuretic factor in the plasma of our patients does not address the question whether larger molecular forms of this factor are present. Third, the protocol used in patients with congestive heart failure was shorter than the protocol conducted in the normal subjects. In patients with heart failure, the 1 h period of  $-20$  mm Hg was deleted to ensure patient comfort and cooperation. We do not believe that prolonging the protocol would have altered the findings in the patients with heart failure. Fourth, our normal subjects were younger than the patients with heart failure. It is possible that age contributed to the blunted responsiveness of the sympathetic nervous system, the renin-angiotensin-aldosterone system and vasopressin in the patients with heart failure because baroreceptor sensitivity may be decreased in older persons (42,43). However, it is very unlikely that age would sufficiently explain the absence of change in these hormones in patients with heart failure during lower body negative pressure.

**Conclusions.** In both normal subjects and patients with chronic congestive heart failure, the plasma concentration of atrial natriuretic factor decreases when central venous pressure is reduced. Incremental lower body negative pressure is accompanied by increases in the plasma levels of norepinephrine, vasopressin and renin activity in normal subjects but not in patients with heart failure. From these data we conclude that the responsiveness of atrial natriuretic factor to reduction in right atrial pressure is preserved in patients with heart failure, whereas baroreceptor-mediated increases in the activity of the sympathetic nervous system, the renin-angiotensin-aldosterone system and vasopressin are attenuated or abolished. This imbalance may allow atrial natriuretic factor to modulate vascular resistance and sodium excretion in patients with heart failure during change in posture or volume status.

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